

Claims

What is claimed is:

1. A genetically modified cell comprising:
 - (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and
 - (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.
2. The cell of claim 1, wherein said gene amplification system further comprises a GAL4 upstream activating sequence (UAS) linked to said nucleic acid sequence encoding said therapeutic product.
3. The cell of claim 1 or 2, wherein said chimeric transactivator is oxygen-sensitive.
4. The cell of claim 2, wherein said physiological stimulus is a signal associated with a pathological condition, and wherein said chimeric transactivator of said first exogenous polynucleotide binds to said GAL4 UAS of the second exogenous polynucleotide in response to the signal associated with the pathological condition, resulting in expression of the therapeutic nucleic acid sequence encoding the therapeutic product.
5. The cell of claim 4, wherein said signal is hypoxia associated with ischemia.
6. The cell of any of claims 1 to 3, wherein said gene switch/biosensor encodes an oxygen-sensitive chimeric transactivator and an operatively linked promoter, wherein said oxygen-sensitive chimeric transactivator comprises a GAL4 DNA-binding domain (DBD), an oxygen-dependent, and a p65 activation domain (p65AD); and wherein said nucleic acid sequence encoding a therapeutic product comprises a cardioprotective gene linked to a GAL4 upstream activating sequence (UAS).

7. The cell of claim 6, wherein said therapeutic product is selected from the group consisting of HO-1, superoxide dismutase, phospholamban (PLN) pre-pro-insulin, an anti-cell growth polypeptide, an anti-angiogenesis polypeptide, tPA, erythropoietin, a polypeptide with hypolipidemic activity, a polypeptide that acts on the cholesteryl ester transfer protein and lipase systems, a polypeptide that provides low density lipoprotein receptor replacement, a polypeptide that induces vascular protection and disobliteration of occlusions, and an interfering RNA molecule.

8. The cell of any of claims 1 to 7, wherein said cell comprises a viral vector comprising said first and second exogenous polynucleotides.

9. The cell of claim 8, wherein said viral vector is selected from the group consisting of a adeno-associated virus, an adenovirus, and a retrovirus.

10. The cell of claim 8, wherein said viral vector is adeno-associated virus.

11. The cell of any of claims 1 to 7, wherein said cell comprises a non-viral vector comprising said first and second exogenous polynucleotides.

12. The cell of any of claims 1 to 11, wherein said cell is a pluripotent or totipotent stem cell.

13. The cell of any of claims 1 to 11, wherein said cell is selected from the group consisting of a hematopoietic stem cell, a mesenchymal stem cell (MSC), a muscle derived stem cell, and a bone marrow mesenchymal progenitor cell (MPC).

14. The cell of any of claims 1 to 11, wherein said cell is selected from the group consisting of a muscle cell, a tubular cell of kidney, a type I pneumocyte of lung, a type II pneumocyte of lung, an ependymal cell, a cell from the subventricular zone of the central nervous system, a blood cell, a duct cell of the pancreas, an epidermal cell of the skin, an endothelial cell, a fat cell, an epithelial cell, a neurocell, and a Schwann cell.

15. The cell of claims 1 to 3, wherein said gene amplification system comprises nucleic acid sequences encoding multiple therapeutic products, wherein said therapeutic products are the same or different.

16. The cell of claim 1 or 2, wherein said therapeutic product is a polypeptide that is heterologous to said cell.

17. The cell of claim 1 or 2, wherein said therapeutic product is a polypeptide that is endogenous to said cell.

18. The cell of claim 1 or 2, wherein said physiological stimulus is selected from the group consisting of hypoxia, glucose, a tumor marker, and an atherosclerosis indicator of inflammation.

19. The cell of claim 1 or 2, wherein said physiological stimulus is selected from the group consisting of a cytokine, MCP-1, c-reactive protein, elevated triglyceride level, elevated oxidized LDL cholesterol level, elevated Lp(a) level, elevated homocysteine level, decreased HDL level, and decreased nitric oxide production.

20. The cell of claim 1 or 2, wherein said physiological stimulus-sensitive chimeric transactivator comprises glucose-sensitive element, and wherein said therapeutic product comprises pre-pro-insulin.

21. A method for modifying a tissue, the method comprising the step of: delivering to the tissue a genetically modified cell of any of claims 1 to 20.

22. The method of claim 21, wherein said tissue is selected from the group consisting of myocardium, mesenchymal tissue, pancreatic tissue, liver tissue, and brain tissue.

23. The method of claim 21 or 22, wherein said delivering is carried out *in vitro*.

24. The method of claim 21 or 22, wherein said delivering comprises delivering said cell to a subject *in vivo*.

25. The method of claim 24, wherein said subject is suffering from a condition selected from the group consisting of diabetes, cancer, stroke, pulmonary fibrosis, arthritis, atherosclerosis, and inflammation.

26. A genetically modified stem cell comprising:

(a) a first exogenous polynucleotide comprising:

- (1) a nucleic acid sequence encoding a GAL4 DNA-binding domain,
- (2) a nucleic acid sequence encoding an ODD domain polypeptide,
- (3) a nucleic acid sequence encoding a p65 activation domain,
- (4) two AAV ITRs, and
- (5) an operatively linked promoter; and

(b) a second exogenous polynucleotide comprising six copies of a GAL4 UAS, an E1b TATA element, a therapeutic gene, and two AAV ITRs.

27. A method for modifying a tissue, the method comprising the step of: delivering to the tissue a genetically modified stem cell of claim 26.